

## REMARKS

### **I. Amendments**

**Drawings:** New Figure 2A has been submitted to replace originally filed Figure 2A. The amendment to Figure 2A is made merely to add a sequence identifier to the sequence disclosed therein (SEQ ID NO:1), which was inadvertently omitted to the Figure as originally filed. The amendment does not add or constitute new matter, and is supported by the application as filed.

**Claims:** Claims 5-12, 17-29 and 33 are canceled. New claims 36-48 are added. Claims 1-4, 13-16, 30-32, 34 and 35 have been withdrawn from consideration as directed to non-elected inventions. The newly added claims do not constitute new matter and are completely supported throughout the specification and originally filed claims. More particularly, newly added claims 36-48, drawn to a transgenic mouse whose genome comprises a disruption in the endogenous mouse glucocorticoid-induced receptor gene, a cell or tissue derived from said mouse, and a method of producing said mouse can be found, for example, at page 9, line 1 through page 15, line 20, and at page 51, line 25 through page 54, line 15, of the specification.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, claims 36-48 are pending in the instant application.

### **II. Sequence Compliance**

The Examiner has contended that the instant application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 in that the sequence in Figure 2A does not have a sequence identifier. As noted above, the Applicant has amended original Figure 2A in order to include a sequence identifier, which was inadvertently omitted. Moreover, Applicant submits that the sequence disclosed in Figure 2A is identical to the glucocorticoid-induced receptor gene disclosed in SEQ ID NO:1 in Figure 1. As such, no additional sequences have been added.

The Sequence Listing submitted on July 20, 2002 (originally submitted October 26, 2001), in computer readable format (CRF) and paper, contains all sequences disclosed in the application. Therefore, the Applicant believes that a substitute Sequence Listing in CRF is not

required. Moreover, the content of the paper and computer readable copies of the Sequence Listing submitted on July 20, 2002 are identical. The sequence listing submitted in this application merely presents nucleotide and/or amino acid sequences that appeared in the application as originally filed in accordance with 37 C.F.R. §1.821-1.825, thus no new matter has been introduced into the application.

### **III Rejections**

#### *A. Rejection under 35 U.S.C. § 112, first paragraph*

**Written Description:** The Examiner has rejected claims 5-12, 17-29 and 33 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleges that, while the specification allegedly teaches only one mouse glucocorticoid-induced receptor gene, the claims encompass more than one glucocorticoid-induced receptor gene, and more particularly, encompass any glucocorticoid-induced receptor gene that may exist in each and every species of animal.

The Applicant respectfully traverses the rejection under 35 U.S.C. § 112, first paragraph. However, in light of the cancellation of claims 5-12, 17-29 and 33, the rejection is no longer relevant, and Applicant requests withdrawal of the rejection. The Applicant submits that subject matter of new claims 36-48, drawn to a transgenic mouse whose genome comprises a disruption in the endogenous mouse glucocorticoid-induced receptor gene, cells and tissue obtained therefrom, and a method of making said mouse, is described in the specification in such a way as to convey possession of the invention as claimed.

**Enablement:** The Examiner has rejected claims 5-12, 17-29 and 33 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Specifically, according to the Examiner, the specification, while being enabling for a mouse or mouse cell whose genome comprises a homozygous disruption of the glucocorticoid-induced receptor gene, wherein said mouse exhibits signs of hyperactivity, reduced anxiety, or decreased propensity toward behavioral despair or depression, and wherein the mouse is derived from the F1N1 generation, does not provide enablement for any transgenic non-human animal or a cell of any species or genetic

background with a disruption of any glucocorticoid-induced receptor gene wherein said transgenic cell or animal has any phenotype.

In one aspect of the rejection, the Examiner asserts that due to the unpredictability of the phenotype of transgenics, which includes considerable variation in the level of transgene expression between animals, leading to varying phenotypes, the transgenic animal as claimed is not enabled by the specification in that it does not recite a phenotype resulting from the disruption. Further, the Examiner states that transgene phenotypes were variable between animal species. The Examiner also states that the specification is not enabling for a heterozygous disruption of the glucocorticoid-induced receptor gene in the transgenic mouse with the phenotypes as encompassed by claims 17-23, due to this unpredictability.

In another aspect, the Examiner has rejected the claims based on the lack of targeted gene insertion technology available for any species other than mouse at the time of filing, and alleged lack of disclosure of any such technology in the instant specification. According to the Examiner, ES cells capable of providing germline chimeras were not available in species other than mouse.

In another aspect of the rejection, the Examiner states that the specification fails to enable disrupting any glucocorticoid-induced receptor gene in a mouse or any other species or a cell other than a mouse cell, due to an alleged lack of disclosure of other species of glucocorticoid-induced receptor.

The Examiner further asserts that the specification does not enable making or using any transgenic mouse comprising a disruption in the glucocorticoid-induced receptor gene wherein the mouse is of any genetic background, and wherein the mice exhibit hyperactivity, reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression, in that the state of the art at the time of filing was that the genetic background greatly influenced the performance of a mouse in the tail suspension test. Further the Examiner asserts that genetic background and laboratory conditions may affect results of various behavioral test protocols.

The Applicant respectfully traverses the rejection. However, the Applicant has cancelled claims 5-12, 17-29 and 33, thus making the rejection under 35 U.S.C. § 112, first paragraph no longer relevant.

New claims 36-48 are drawn to a transgenic mouse whose genome comprises a homozygous disruption in the endogenous mouse glucocorticoid-induced receptor gene, wherein the transgenic mouse lacks production of functional glucocorticoid-induced receptor and exhibits hyperactivity, reduced anxiety, decreased propensity toward behavioral despair, or decreased propensity toward depression, a method of making the mouse and a cell or tissue obtained therefrom. The Applicant contends that new claims 36-48 are fully enabled by the instant specification. In particular, the Applicant has described the transgenic mouse, cells and methods as claimed in the new claims 36-48 so that one skilled in the art would be apprised of how to make and use the transgenic mouse and cells and tissues as claimed.

More particularly, the genome of the transgenic mouse as presently claimed comprises a homozygous disruption in the mouse glucocorticoid receptor gene, which disruption inhibits production of the glucocorticoid-induced receptor, resulting in a transgenic mouse exhibiting hyperactivity, reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression. The instant specification clearly describes how to produce such a disruption in a transgenic mouse (see Figure 2 and page 51-54 of the specification) in order to create the transgenic mouse exhibiting the phenotype as claimed. Moreover, one skilled in the art would be able to easily determine and interpret the phenotype, regardless of genetic background, in light of the knowledge in the art, using standard behavioral tests, which are described in the specification (see pages 21-25).

The Applicant respectfully submits that the references cited by the Examiner to demonstrate lack of enablement for behavioral phenotypes are not sufficient. Crabbe *et al.* (1999, *Science* Vol 284, pages 1670-1672) determined that genotype accounted for most variability between studies. Furthermore, Yoshikawa *et al.* (2002, *Genome Research*, Vol. 12, pages 357-366), is more applicable to the use of the tail suspension test in the investigation of antidepressant drugs. The pending claims no longer relate to such an animal model. The transgenic mouse exhibiting the claimed behavioral phenotypes is sufficiently described in the instant specification, and appropriate age- and gender-matched controls have been used to rule out the problems in the determination of behavioral phenotypes cited by the Examiner.

In view of the cancellation of claims 5-12, 17-29 and 33, and the submission of new claims 36-48, which are completely enabled by the specification as originally filed, the rejection

under 35 U.S.C. § 112, first paragraph, is no longer relevant. Therefore, the Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

***B. Rejection under 35 U.S.C. § 112, second paragraph***

Claims 5-12, 17-29 and 33 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner alleges that it is not clear if the claims are meant to encompass all genes that are inducible by glucocorticoids, or if they are referring to genes with a specific homology and functional similarity to the glucocorticoid-induced receptor encoded by SEQ ID NO:1. The Applicant respectfully traverses the rejection, in that the glucocorticoid-induced receptor gene has been sufficiently defined in the instant specification. In any case, the Applicant has cancelled claims 5-12, 17-29 and 33.

The Applicant submits that new claims 36-48 are definite, and particularly point out and distinctly claim the subject matter regarded as the invention. In particular, claims 36-48 make clear which gene is disrupted by the present invention, namely the endogenous mouse glucocorticoid-induced receptor gene, as recited in the present claims and described and defined in the instant specification.

As the rejection under 35 U.S.C. § 112, second paragraph, is no longer relevant as a result of the cancellation of claims 5-12, 17-29 and 33, and new claims 36-48 are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph, Applicant requests withdrawal of the rejection.

***C. Rejection under 35 U.S.C. § 103***

Claims 5-10 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Capecchi, 1994, *Scientific American*, 270, pp34-41 (“Capecchi”) in view of Harrigan, 1991, *Mol. Endocrinol.*, 5, pp 1331-1338 (“Harrigan”). The Applicant respectfully traverses this rejection. However, in view of the cancellation of claims 5-10, the rejection under 35 U.S.C. § 103 is no longer relevant.

The Applicant submits that new claims 36-48 are non-obvious over the teachings of the prior art references. More particularly, the claimed invention relates to the *in vivo* mammalian characterization of the function of the mouse glucocorticoid-induced receptor gene, and provides transgenic mice and cells, the genomes of which comprise disruptions in the endogenous

glucocorticoid-induced receptor gene, and methods of making the mice, all of which are not obvious in view of the sole or combined teachings and disclosures of the references cited by the Examiner.

According to the Examiner, Capecchi discloses transforming a cell with a nucleic acid construct comprising a disruption in the *HoxA-3* gene, resulting in an inactivating insertion of a selective marker gene into the endogenous *HoxA-3* locus, and using said cell to generate a mouse whose genome comprises a disruption in the *HoxA-3* gene.

Harrigan, as characterized by the Examiner, merely discloses the cloning of the mouse glucocorticoid-receptor gene.

In order to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria: there must be some suggestion or motivation to modify a primary reference or combine reference teachings; there must be a reasonable expectation of success; and the prior art reference(s) must teach or suggest all the claim limitations. See MPEP §2143. The Applicant contends that the prior art references cited by the Examiner are not sufficient to establish a *prima facie* case of obviousness.

The Examiner asserts that the ordinary artisan would have been motivated to combine the teachings of the prior art references to determine the role of the glucocorticoid-induced receptor gene in a mouse as it was an art-recognized goal to determine the physiological role of a gene of interest by generation of a knockout mouse. The Applicant respectfully disagrees. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See MPEP 2143.01. However, claims 5-10 have been canceled. The Applicant submits that neither Capecchi nor Harrigan suggest the desirability of disrupting the glucocorticoid-induced receptor gene in a mouse as presently recited in claims 36-48. Therefore, the Examiner has failed to provide sufficient evidence in the prior art references of the motivation or suggestion to combine the prior art references required to establish a case of *prima facie* obviousness.

Further, the Applicant submits that the Examiner has failed to show that one of ordinary skill in the art would have a reasonable expectation of success to make a glucocorticoid-induced receptor knockout mouse based on the combined disclosures of the prior art references, and in particular, based on the disclosure of Capecchi, who discloses a transgenic mouse comprising a

*HoxA-3* gene disruption, and Harrigan, who provides the sequence for the mouse glucocorticoid-induced receptor gene.

Finally, in order to establish a *prima facie* case of obviousness, the Examiner must also show that the prior art references teach or suggest all of the claimed limitations. As described above, the disclosure of Capecchi relates to a transgenic mouse having an inactivating disruption in a *HoxA-3* gene. Harrigan is limited to providing disclosure related to the nucleic acid sequence of the mouse glucocorticoid-induced receptor gene in particular.

However, neither Capecchi nor Harrigan, alone or in combination, teaches all of the limitations as presently claimed in claims 36-48. As acknowledged by the Examiner, Capecchi provides no disclosure or teaching of the glucocorticoid-induced receptor gene described in the instant specification, and in particular does not disclose a specific phenotype of the transgenic mouse comprising a disruption in said gene, particularly a phenotype of hyperactivity, reduced anxiety, reduced propensity toward behavioral despair or reduced propensity toward depression, as claimed by the present invention. Likewise, Harrigan does not provide any teaching or suggestion relating to targeted disruptions in any gene, particularly in the mouse glucocorticoid-induced receptor gene as presently claimed. More particularly, the disclosure of Harrigan fails to provide any teaching or suggestion that relates to the transgenic mice and cells as recited in the pending claims.

Taken together, the disclosures Capecchi and Harrigan are devoid of any teaching or suggestion of the transgenic mice and cells as recited in the pending claims. More particularly, the disclosures of Capecchi and Harrigan, alone or combined, do not teach or suggest in any way transgenic mice comprising disrupted glucocorticoid-induced receptor genes, wherein such transgenic mice exhibit a phenotype, and in particular exhibit a phenotype of hyperactivity, reduced anxiety, reduced propensity toward behavioral despair or reduced propensity toward depression. Further, these prior art references do not disclose the tissues and cells comprising the disrupted mouse glucocorticoid-induced receptor gene as claimed by the present invention.

Claims 5-10 were also rejected under 35 U.S.C. § 103 (a) as being unpatentable over Beach, 1999, *USPN*, 5,919,997 (“Beach”) in view of Harrigan, 1991, *Mol. Endocrinol.*, 5, pp 1331-1338 (“Harrigan”). The Applicant respectfully traverses this rejection. However, in view of the cancellation of claims 5-10, the rejection under 35 U.S.C. § 103 is no longer relevant.

According to the Examiner, Beach discloses transforming a cell with a nucleic acid construct comprising a disruption in the INK4 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous INK4 locus, and using said cell to generate a knockout mouse whose genome comprises a disruption in the INK4 gene. Harrigan, as noted above, relates to the cloning of the mouse glucocorticoid-induced receptor gene.

However, Beach does not teach transgenic mice or cells comprising a disruption in the glucocorticoid-induced receptor gene as claimed by the present invention. Further, Beach does not teach the production of transgenic mice comprising disruptions in the glucocorticoid-induced receptor gene according to the instant invention, wherein the transgenic mice exhibit hyperactivity, reduced anxiety, reduced propensity toward behavioral despair or reduced propensity toward depression.

Like Beach, the disclosure of Harrigan is deficient in teaching or suggesting the transgenic mouse as claimed by the present invention, and, in particular, a transgenic mouse comprising a disruption in the glucocorticoid-induced receptor gene as currently claimed, or cells or tissue obtained from said mouse, and in particular does not disclose any teachings relating to the phenotype of such mice as claimed.

Taken together, the disclosures of Beach and Harrigan are absent of any teaching or suggestion of disrupting the glucocorticoid-induced receptor gene of the instant invention in a mouse, and, in particular, are deficient of any teaching or suggestion of the transgenic mice, cells, tissue, and methods recited in the pending claims. More particularly, the disclosures of Beach and Harrigan, alone or in combination, do not teach or suggest in any way the transgenic mice comprising disrupted glucocorticoid-induced receptor genes, which exhibit hyperactivity, reduced anxiety, reduced propensity toward behavioral despair or reduced propensity toward depression, methods of producing such transgenic mice, or tissues and cells obtained from such transgenic mice. For these reasons, in addition to the reasons set forth above in response to the prior obviousness rejection, claims 36-48 are not obvious in view of the prior art references.

As the obviousness rejections are no longer relevant as result of the cancellation of claims 5-10, and new claims 36-48 are not obvious in view of the teachings of Capecchi and Harrigan, and are also not obvious in view of the teachings of Beach and Harrigan, the Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 103.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-356.

Respectfully submitted,

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Kelly L. Quast  
Kelly L. Quast, Reg. No. 52,141

Deltagen, Inc.  
700 Bay Road  
Redwood City, CA 94063  
(650) 569-5100